RENAL-SELECTIVE PRODRUGS FOR CONTROL OF RENAL SYMPATHETIC NERVE ACTIVITY IN THE TREATMENT OF HYPERTENSION

Abstract

Renal-selective prodrugs are described which are preferentially converted in the kidney to compounds capable of inhibiting synthesis of catecholamine-type neurotransmitters involved in renal sympathetic nerve activity. The prodrugs described herein are derived from inhibitor compounds capable of inhibiting one or more of the enzymes involved in catecholamine synthesis, such compounds being classifiable as tyrosine hydroxylase inhibitors, or as dopa-decarboxylase inhibitors, or as dopamine-β-hydroxylase inhibitors. These inhibitor compounds are linked to a chemical moiety, such as a glutamic acid derivative, by a cleavable bond which is recognized selectively by enzymes located predominantly in the kidney. The liberated inhibitor compound is then available in the kidney to inhibit one or more of the enzymes involved in catecholamine synthesis. Inhibition of renal catecholamine synthesis can suppress heightened renal nerve activity associated with sodium-retention related disorders such as hypertension. Conjugates of particular interest are glutamyl derivatives of dopamine-β-hydroxylase inhibitors, of which N-acetyl-γ-glutamyl fusaric acid hydrazide (shown below) is preferred.